June 19, 1953

Dear Aaron:

Your note of the 18th just arrived.

Parts of your letter are rather disturbing. I don't know why either of us should be "angry" at either Hayes or Jim. I have a hunch that Jim is annoyed at me because I sent him an answer to one of his letters (anent the paper in PNAS) which he may never have received, judging from some of the remarks Dave Skaar brought back— if my letters can reach him, I'll try to patch this up. I will admit a certain annoyance (but not anger) at what seems to me to be a certain prematurity of publication, which is bound to muddy the waters somewhat. (But these have never been so very clear that there will be a great loss in the long run). If Hayes has forgotten (at least there was no mention of it in his CSH ms.) it was not long ago that he was espousing lambda as the vector of K-12 recombination, and after that a very limited transduction of isolated factors, and then (with Watson) the more or less independent transmission of single chromosomes, and now (in the CSH ms.) at least the occasional (and statistically far from random) joint transmission of "several chromosomes" from the same parent. It is not hard to see what the extrapolation of this time series will lead to. However, I would be sorry to see the same hierarchical imposition of orthodoxy in this field as certain of our mutual acquaintances have submitted to in phage, and fair argument is always healthy. By and large, Hayes' ms. seemed to match this criterion. Of course, I have no way of measuring the tone of his (or perhaps worse, Jim's) remarks, and if there was some occasion for indignation at this, it is an inference I would be sorry to have to draw from your letter.

I hope you have (and Ed and Szilard, and whomever you meant by "intelligent" people[or otherwise] at the Symposium) have not read any profound meaning into our staying at home. It was hard to see what profit we could get from it— the pleasure of seeing everybody being matched by the nuisances of travelling, and the usual sequelae of exhaustion from such symposia— and we were rather tired both from rigors of trips and mss. this Spring, and prospects of a hot summer (which are being realized with a vengeance already) at the end of which we are planning to move into a new house. These were sufficient reasons; what I am about to mention would not have been by themselves, and wha would not have kept us home by itself. I am personally convinced that Hayes' formulation is not correct, on the one issue susceptible to decision: the timing of the loss of the markers of the F+ parent from the progeny. The data are rather involved (though most of them have actually been published in the Cold Spring Harbor Symposium for 1951) and have to do mostly with the diploids. Let me try out a piece of confusing terminology on you: in any cross whose polarity is determinate we will call the F+ side "paratypic", and the F- side "orthotypic" [this is entirely tentative, and I would welcome suggestions for any other terms less prejudicial than "gene acceptor" or male/female. The polarity of Mal elimination, as of

segregation of markers in prototrophs, is controlled largely by the F status. ~~As a rule,~~ In diploids heterozygous for most other markers, Mal is almost invariably hemizygous, and as a rule it is the paratypic (F+) allele that is missing. However about 15-20% of the diploids, though still hemizygous for Mal, have eliminated the orthotypic allele. In addition, in several cases, where both Mal and the closely linked S marker were available, diploids have been found which are crossovers between Mal and S, but where Mal was paratypic, S orthotypic, though both still hemizygous. It is difficult to accomodate orthotypic elimination into a scheme where markers should be missing, if at all, in the F+ gametes, and as far as I can see, impossible to explain the crossovers except by a post-zygotic (and post-crossing-over) elimination. I imagine that elimination occurs by the breakage of a specific locus on an paratypic chromosome, but that prior crossing-over between this locus and Mal (or between Mal and S in a few cases) accounts for the saving of the paratypic allele at the Mal locus in 15-20% of the diploids.

This is probably the most clearcut evidence on the situation, but it is bolstered by a number of odds and ends. However, these are not quite ready for publication, and I am not sorry that we did not feel obliged to bring them into print prematurely for reasons extraneous to the scientific issue. There are, on the other hand, quite a number of inconsistencies in the W-H scheme (e.g. gross inequalities in the frequencies of complementary crossovers between linked markers on "unselected chromosomes") and they cannot all be explained away by adding another chromosome and with it several additional indeterminate parameters (i.e. probabilities of transmission with and without co-transmission of other chromosomes). However, as we have not offered a positive scheme that purports to explain all of the data in a precise way, this is not a constructive criticism. Most of our diploid data has not been published, and owing to the complexity and the absence for most of them of any definite contrasting hypotheses probably will not be, so that W&H have not had an opportunity to study how well it could be fitted to their scheme. However, my own attention has been attracted to post- rather than pre-zygotic peculiarities from the first isolations of the diploids because it was painfully obvious that they were not segregating in random ratios for the markers for which they were heterozygous, aside from their hemizygosity for Mal-S. These two peculiarities could be most economically unified by assuming Mal-S to be on the same chromosome as, e.g., Mtl and Xyl. On the one hand, the elimination of Mal-S would obscure the linkage to some degree (though some interaction is obvious); on the other hand, the alleles on the partly deficient chromosome (after elimination) could not show up in viable haploid segregants without a prior crossover between Mtl and Xyl and the deficient segment. This makes the defect part of, rather than an entire chromosome, but does not settle when the elimination occurs. Before the compatibility (F) story was even suspected, the chief stumbling block to a pre-zygotic elimination hypothesis was that, in any given cross, elimination was usally from one side (paratypic) but occasionally from the other (orthotypic). ~~If, as it would now be expressed,~~ If this were to be explained by the production of occasional incomplete gametes from either side, one would also have to postulate complete gametes from either side as well, and therefore some complete zygotes which never eventuated. (In terms of F polarity, the is even stricter, since this polarity can be experimentally defined.) Rather than postulate a selective mating of deficient with complete gametes (which would have to be both F+:F- and F-:F+ in an F+ x F- cross), which still could not account for the Mal/S crossovers, elimination was supposed to be post-zygotic. The F story promises to illuminate this conclusion, without changing it. One final point: Mal and S have <u>always</u> been hemisygous, Mtl, Xyl, Lac and V_1 have <u>never</u> been in crosses where this would not have been predetermined along W-H's proposals.

So you see, I think that probably Hayes is not right. This is rather a fine point at issue, and by itself would not be worth all the fuss (especially after the semantic obscurities have blown away). But as a challenge that has helped to formulate some concrete alterhative hypotheses, it probably will turn out to

for the best in the long run.

I am not sure (while admitting the possibility) that someone or other may be trying to fan this controversy and divert it to his own purposes but whether this is true or not, I am sure that none of the principals are so involved. I hope you are not yourself misled into any unwitting encouragement of it.

Our immediate plans are somewhat unsettled. Any chance of you guys paying us a visit? We'd love to have you. If not we might conceivably drop down ourselves, but is Chicago the place to go to in the summer?

Sincerely

Joshua Lederberg